

# Corticosteroid Therapy In Childhood Asthma

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■ *Fortunately, nearly all cases of asthma in childhood can be managed successfully without the use of adrenal corticosteroids. However, when used properly the corticoids enable that small group of children who have not responded to traditional allergic management to lead normal lives. The action of these compounds is a pharmacologic and not a physiologic one. The adrenal corticosteroids suppress the symptoms of childhood asthma but in no way serve as curative agents of allergic disease.*

THE ADRENAL CORTICOSTEROIDS were introduced as pharmacological agents in clinical medicine 16 years ago.<sup>36</sup> These anti-inflammatory substances now are being used extensively in pediatrics in the management of blood dyscrasias,<sup>52</sup> childhood nephrosis,<sup>9</sup> connective tissue disorders<sup>51</sup> and traditional "allergic" diseases—asthma and atopic dermatitis.<sup>53,56,61</sup> This review is an assessment of the role of the corticosteroids in childhood asthma.

## Steroids—Structural Relationships

Steroids are lipid substances which are distributed widely in nature. A large number of them are produced by the adrenal cortex but, of these, hydrocortisone (cortisol) is the chief natural compound with anti-inflammatory activity. Its structure and the configuration of some common synthetic agents which share the basic steroid molecular structure necessary for anti-inflammatory activity are shown in Figure 1. All anti-inflammatory steroids are members of the carbon-

21 glucocorticoid series and have hyperglycemic, protein-wasting, ACTH-suppressing and eosinopenic effects. Hydrocortisone is transported in the circulation in the 17-hydroxycorticoid fraction loosely bound to plasma protein. Ninety per cent of it is reduced and conjugated in the liver with glucuronic acid and excreted in the urine by glomerular filtration.

The physiologic and pharmacologic effects of all these compounds are similar, with minor variations. The pharmacologic potency of any corticoid is dependent on the intensity of the end-organ response as well as the survival time of the corticoid in an active state in body fluids. The relative anti-inflammatory potencies of various steroid preparations are shown in Table 1.

Corticosteroid preparations can be administered via the oral, intramuscular, intravenous, rectal or inhalation route. With the administration of oral steroid medication, the peak blood concentration occurs in four to eight hours, with subsequent rapid decline. Absorption by the intramuscular route is variable, depending on the vehicle in

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TABLE 1.—*Relative Anti-Inflammatory Potencies, Showing Amount of Various Corticosteroid Preparations Needed to Have Effect Equal to 25 mg of Cortisone*

	Milligrams
Cortisone .....	25
Hydrocortisone .....	20
Prednisone .....	5
Prednisolone .....	5
Methyl prednisolone .....	4
Triamcinolone .....	4
Dexamethasone .....	0.75

which the drug is contained. Some intramuscular preparations are absorbed over a period of several weeks. Systemic absorption also occurs in varying degrees when the drugs are administered by inhalation.

In this review, the term *steroid* or *corticosteroid* will be used interchangeably with hydrocortisone, the naturally-occurring hormone of the adrenal cortex after which many synthetic anti-inflammatory agents have been patterned.

#### Asthma—Basic Concepts

Asthma, a reversible clinical syndrome, consists of cough and wheezing due to smooth muscle spasm, mucosal edema and excess mucus production in the bronchial tree. Many clinicians consider this disease to be episodic, but most children with asthma have underlying respiratory symptoms between attacks, particularly if the illness is not under good control. These "continuity symptoms" are coughing or wheezing with exertion and coughing at night. There are also usually associated symptoms of nasal allergic sensitivity—nasal itching, sneezing and rhinorrhea.<sup>16</sup>

Asthma in childhood is considered to be an allergic disorder. Allergy, a term first used early in this century by von Pirquet,<sup>64</sup> describes the "altered reactivity" of an organism upon reexposure to a foreign substance or allergen. Recently, Gell and Coombs<sup>14</sup> classified the allergic reactions into four categories (Types I to IV), depending upon the basic mechanisms that occur. The Type I reaction, characterized by the combination of antigen (allergen) with antibody which is already present on the cell surface, subsequently leads to the release of such mediators as histamine, which then produce a variety of pharmacologic effects. The Type II allergic reaction is characterized by the combination of antibody with the tissue cell, or antigen, or hapten which has been intimately associated with the cell (auto-immune hemolytic anemia). Type III reactions depend on antigen-

antibody complexes in antigen excess (serum sickness), and Type IV reactions encompass the delayed hypersensitivity phenomena (tuberculin reaction).

Atopy is a term which was introduced by Coca in 1923<sup>11</sup> to describe the type of hypersensitivity which is peculiar to man, subject to hereditary influence, associated with circulating antibody (reagin) and manifesting such clinical syndromes as hay fever and asthma. Atopy encompasses one part of the broad field of allergy. Human atopic reactions are Type I allergic reactions and underlie most cases of childhood asthma. Atopic persons have the capacity to become sensitized to a number of different inhalant and food substances or allergens which are innocuous to more than 90 per cent of the general population. They also usually have family histories of atopic disorders and increased numbers of eosinophiles in nasal secretions and peripheral blood. It is theorized that, in atopic persons, the allergen enters the body via a natural route—respiratory tract, gastrointestinal tract or skin—and evokes the production of circulating reaginic antibody which also has skin sensitizing activity. This antibody becomes fixed to cells in the "shock organ"—nasal mucosa, bronchioles, skin. On subsequent exposure, the allergen reacts with the reaginic antibody on the cell surface, and a number of pharmacologic mediators are released (histamine, slow-reacting substance, bradykinin and probably others). Through their effects on blood vessels, mucosal glands and smooth muscle, these mediators produce an inflammatory response. Considerable basic investigation is being done on other immune phenomena in the allergic reaction which, presumably, underlie the mechanisms that operate in most cases of childhood asthma.<sup>38</sup>

The most common environmental allergens are house dust, animal danders, pollens and molds. In food allergy, which is less common, the immunologic mechanisms are more obscure since there is little correlation between the presence of specific reaginic antibody on skin testing and clinical symptoms. In both inhalant and food cases, one must distinguish between the underlying specific allergenic factors in asthma and a host of non-specific "trigger" factors<sup>16</sup> such as chemical irritants, climatic changes, respiratory infections, emotional factors, autonomic reflex phenomena and probably many other unknown variables.

Most children with asthma respond to the tra-

ditional approach of removing as much of the offending allergen as possible, followed by injection therapy in selected cases. The remaining respiratory symptoms can usually be controlled with bronchodilators. Even though some of these children may have constant mild symptoms and periodic acute exacerbations, they are able to lead essentially normal lives. A few, however, continue to have difficulty in spite of good allergic management. Some continue to be extremely sensitive to usual allergens; others are not particularly reactive either clinically or on skin testing. Unrecognized food allergy may be present. Emotional factors are often quite prominent in this group, but it is usually difficult to determine whether they are of etiologic significance or represent a reaction of the child to chronic illness.

When chronic asthma becomes severe, the airway becomes extremely "irritable" and may react in an adverse way to a variety of stimuli which are ordinarily innocuous. At this point one is faced with a chronic and disabling illness which can have a tremendous impact on the child and his family. It is in this small group of children in whom traditional allergic management fails or is only partially successful, that steroid therapy deserves consideration.

#### **Mechanism of Corticosteroid Action in Asthma**

Theoretically, corticosteroids may interrupt the sequence of immunologic events which lead to the production of symptoms in asthma by three mechanisms: direct inhibition of tissue inflammation, antagonism of histamine or its precursors, or by suppression of antibody formation.

#### **Direct Inhibition of Tissue Inflammation**

The effects of hydrocortisone in tissue inflammation have been studied extensively. Experimentally, radioactive hydrocortisone has a half-life in the blood of about 45 minutes and exerts its anti-inflammatory effects in tissues within the first hour after injection. Apparently, the level of hydrocortisone necessary to inhibit inflammation is present in tissue for a shorter period than the duration of the anti-inflammatory effect; this may be due to the initiation of a response in the connective tissue fibroblast.<sup>20</sup> The corticosteroids inhibit capillary permeability, help to reduce transudation of fluid from the vascular tree and inhibit the synthesis of chondroitin sulfuric acid in connective tissue ground substance.<sup>2</sup>

The cells of the hemopoietic system are intimately involved in non-specific as well as allergic inflammatory responses and are affected in a variety of ways during therapy with steroid hormones. There is an increase in polymorphonuclear neutrophils in the circulation. Their survival time is increased but their ability to phagotize cells and their ameboid activity is diminished. While the role of the eosinophile in inflammation is not clear, it is well known that steroids depress the circulating levels of these cells. Lymphocytes are intimately involved in delayed hypersensitivity reactions (Gell and Coombs Type IV) and are depressed in the blood and tissues during corticoid therapy. The action of the corticosteroid hormones on tissue inflammation appears to be the major factor in relief of clinical symptoms in asthma.

#### **Antagonism of Histamine or Its Precursors**

Corticosteroids have little effect on the release of histamine; they do not inhibit the rapid pharmacologic action once it is present in the circulation, and they are not beneficial in the immediate treatment of the human anaphylactic reaction. Goth,<sup>30</sup> however, has shown that they do prevent the reaccumulation of histamine in tissues after previous discharge. Mast cells, possibly a major source of histamine in the allergic reaction, are altered by hydrocortisone—they diminish in number, become vacuolated and acquire irregular outlines. The size of the granule changes, and the uptake of radioactivity labeled sulfate is inhibited.<sup>2</sup>

Schayer<sup>49</sup> recently proposed that there are two types of histamine which play a role in the inflammatory response—*extrinsic* histamine obtained from mast cells and released into the general circulation, and *intrinsic* histamine formed through the action of histidine decarboxylase in vascular endothelial cells at the precapillary arteriolar level. Intrinsic histamine exerts its effect locally, is not affected by systemic antihistamines and is under the regulation of the glucocorticoid hormones. Clinically, the response of most cases of asthma to antihistamines is discouraging and, unless one accepts Schayer's theory, the role of steroids on histamine metabolism is probably a subsidiary one.

#### **Suppression of Antibody Formation**

Since reaginic antibody (reagin) plays a role in human atopic disease, it is interesting to speculate about steroid suppression of antibody formation as a factor in diminishing the allergic reaction

in asthma. Studies concerning this point have been performed in animals, using various antigen-antibody systems. In rabbits treated with corticoids, antibody production was inhibited during the primary response following antigenic stimulation. This effect, less pronounced but still present, followed secondary anamnestic stimuli.<sup>22</sup> Steroids apparently inhibit antibody synthesis and do not increase antibody catabolism, since antibody disappearance curves in passively sensitized cortisone-treated animals are similar to the curves for untreated controls.<sup>22</sup> The steroids, as mentioned, reduce the number of tissue lymphocytes and probably suppress antibody production through their effects on these cells.

General or local anaphylactic reactions depend upon the "fixation" of antibody by cells and subsequent release of chemical mediators following antigenic stimulation (Gell and Coombs Type I allergic reactions). The corticoids inhibit anaphylactic reactions in some species, such as the mouse, where vascular permeability factors, cellular aggregation and other mechanisms may be prominent. However, in the guinea pig and in man the effects of anaphylaxis are more dependent on the chemical mediators and are little influenced by steroids.<sup>22</sup> Adrenal cortical hormones do not protect passively sensitized guinea pigs from systemic anaphylaxis or local passive cutaneous anaphylaxis (PCA) which requires minute amounts of antibody.<sup>46</sup> In humans, the local anaphylactic reaction of the allergy skin test, which is dependent upon the presence of reaginic antibody, is also not affected by steroid therapy.<sup>40</sup>

Studies to date have shown partial inhibition, but never complete suppression, of antibody synthesis during corticoid treatment. With the dosages used currently in clinical situations, it is unlikely that this mechanism is very important in allergic reactions.<sup>37</sup>

### Short-Term Therapy

Corticosteroids can be used effectively in the management of the acute asthmatic attack. Large doses, given over a period of seven to ten days and tapered rapidly or stopped abruptly may prevent hospitalization or shorten it. Many of the dangers of chronic steroid therapy can be avoided when the duration of treatment is less than three to four weeks; there is laboratory evidence of a normal adrenal pituitary axis response soon after cessation of therapy. However, it must be emphasized that

the normal response to stress of the adrenal glands may be suppressed for several months afterward,<sup>63</sup> so that close follow-up during this time is mandatory.

Repeated short courses of steroids should not replace good allergic management, and vigorous attempts at control of acute episodes with bronchodilator medication should always be made. The treatment of severe status asthmaticus demands adequate hydration, expectorants, oxygen, bronchodilation—often, inhalation therapy to deliver moisture and medication to the bronchial tree; and, rarely, use of a bronchoscope for removal of secretions. Corticoids are of undoubted therapeutic benefit but should not be relied upon exclusively. Experimentally, they can cause cellular changes within one to two hours<sup>20</sup>; however, in a severe asthmatic attack clinical improvement does not usually occur that rapidly. With a comprehensive treatment regimen, it is often difficult to assess the role of hydrocortisone in the improvement of clinical symptoms.

Large doses of steroids given over a short period in conjunction with other therapeutic measures, can be of aid in distinguishing between a reversible and an irreversible pulmonary disease process. Tooley and Nadel<sup>60</sup> studied the pulmonary function in a group of ten children with severe asthma before and after a therapeutic regimen which included large doses of steroids for one to two weeks. They found evidence of severe obstructive airway disease in all patients before treatment. After therapy, all of them had normal pulmonary function. At present, childhood asthma appears to be a reversible process but pulmonary function studies of more patients over a longer period will be necessary to resolve this issue.

### Continuous or Long-Term Steroid Therapy

The initial enthusiasm for the pharmacologic benefits of the adrenal corticoids was dampened considerably by the serious adverse side effects which may occur with long-term use.<sup>29</sup> These untoward effects must be weighed carefully when considering steroid therapy in any illness. In childhood asthma there are two great dangers in the use of these agents: adrenal insufficiency and growth suppression. The other common major hazards to steroid therapy are well defined, and some unusual complications have been described.

### Adrenal Insufficiency

The effect of exogenous corticoids on the pituitary-adrenal axis is the major reason why these drugs must be used with great caution. Exogenous administration of hydrocortisone inhibits the secretion of ACTH by the pituitary gland resulting in diminished output of glucocorticoids and adrenal atrophy. The extent to which this occurs depends on the dosage of corticoid medication, the type and duration of treatment and unknown variables in the individual patient.<sup>63</sup> Thus, abrupt cessation of continuous steroid therapy or the development of sudden stress in a patient receiving corticoids may result in the classic symptoms of adrenal insufficiency—for example, irritability, headache, abdominal pain, vomiting, weakness, pallor, shock and death.<sup>23</sup>

Urine and serum hydroxycorticoid levels before and after ACTH stimulation provide laboratory evidence for adequate adrenal function. Ketogenic steroid levels following administration of methapyrapone (SU 4885) help to test the adequacy of pituitary ACTH function.<sup>25,28</sup> Wood,<sup>66</sup> however, pointed out that failure of the pituitary-adrenal axis to respond to stress cannot be excluded by an ACTH stimulation test. Laboratory evidence of a normal pituitary-adrenal axis does not rule out the possibility of relative adrenal insufficiency in the event of a severely stressful situation.<sup>63</sup> There have been reports on the development of acute adrenal insufficiency at surgical operation that is done during or following cessation of steroid therapy.<sup>24,47</sup> The risks of long-term steroid treatment begin to occur when the duration of therapy exceeds three to four weeks.

### Growth Suppression

Retardation of growth is shown by patients with Cushing's syndrome who have excess circulating 17-hydroxycorticoids.<sup>59</sup> The adrenal corticosteroids suppress linear growth through an inhibitory effect on epiphyseal cartilage which may be the result of antagonism with growth hormone.<sup>4,35</sup> Growth rates of children with severe allergic disease also may be diminished, but increase decidedly when allergic symptoms are ameliorated.<sup>12</sup> In 1956, Blodgett and coworkers<sup>6</sup> administered cortisone in dosages greater than 45 mg per square meter of body surface per day and produced a reduction in growth rates within several weeks. When the drug dosage was reduced below this critical level or was stopped entirely, a growth spurt with a return to normal levels ensued. Van

Metre and coworkers<sup>62</sup> studied the comparative growth-inhibiting effects of a number of different steroid preparations in childhood asthma and found that prednisone and methyl prednisolone had growth suppressive effect at a dosage of 5 mg per square meter of body surface per day compared with 55 mg per square meter for cortisone. Since the difference is more than ten-fold and the anti-inflammatory activity of cortisone is one-fifth that of prednisone, cortisone appears to be the drug of choice for patients in whom growth suppression is apt to occur.

Obviously it would be helpful to have knowledge of the growth pattern of the child before beginning continuous steroid therapy, but it is most important to have frequent and careful height measurements of the child while he is receiving these drugs.

The more common complications of chronic steroid therapy are well known to most physicians:

- The typical cushinoid features of hyperadren-alism.<sup>58</sup>
- Osteoporosis, because of the anti-anabolic effect of hydrocortisone on protein metabolism leading to a deficiency of bone matrix, and because of impaired calcium absorption and increased losses of calcium and phosphorus in the urine and stool.<sup>44</sup> Osteoporosis is more commonly observed in middle-aged or older adults and in children with such diseases as rheumatoid arthritis, where immobilization is a prominent factor.<sup>18</sup> It is not usually a serious problem during steroid therapy in chronic asthma.
- Hypertension—blood pressure should be monitored regularly.<sup>43</sup>
- Electrolyte abnormalities—sodium retention and potassium loss—which are much less common since the advent of the newer steroid analogues.<sup>42</sup>
- Increased glyconeogenesis, which can lead to and increase in blood sugar, glycosuria and symptoms of diabetes.<sup>13,19</sup>
- Gastrointestinal bleeding which can result from the effect of the steroid hormones on acid secretion and mucosal resistance.<sup>31</sup>
- Altered personality patterns and frank psychotic episodes.<sup>10,27</sup> A patient's emotional status should be assessed before initiating long-term therapy.
- Susceptibility to infection is increased in certain patients who receive continuous steroid therapy.<sup>26,45</sup> These patients usually have severe dis-

ease processes which also alter host resistance (but this factor does not exist in asthma). Corticoids which suppress the local inflammatory response to infection may also alter the host's immune response to the infecting agent. For example, steroids can suppress the delayed hypersensitivity response to tuberculin and cause activation and spread of a latent tuberculous process.<sup>45</sup> Any child with asthma in whom long-term steroid therapy is contemplated should have a preliminary tuberculin test,<sup>50</sup> chest x-ray and periodic films of the chest during the course of therapy. The development of overwhelming bacterial lung infections in asthmatic children on prolonged steroid therapy is uncommon. The diagnosis of pneumonia is often difficult to make in an asthmatic patient since the rapidly changing infiltrates seen on the chest film are often due to atelectasis.<sup>39</sup> However, since steroids may suppress the systemic manifestations of infection, this diagnosis should be suspected in any asthmatic patient whose condition deteriorates while receiving them. Although overwhelming viral infections—particularly with childhood exanthemata—have been observed in many steroid-treated disease entities,<sup>32</sup> they are unusual in asthma.

- Other effects: pseudotumor cerebri; acute hemorrhagic pancreatitis<sup>3</sup>; myopathy, seen most frequently with triamcinolone, but also with other preparations<sup>8,65</sup>; posterior subcapsular cataracts (in patients with rheumatoid arthritis<sup>5</sup>); and peculiar skin lesions of panniculitis (following steroid withdrawal in patients with acute rheumatic fever<sup>57</sup>).

Since childhood asthma is a reversible disease with a very low mortality rate, the reasons for initiating continuous steroid therapy must be critically examined. The corticoids must not be started until every suspected underlying cause has been investigated thoroughly. It is difficult, if not impossible, to interpret the effects of a regimen for allergic disease while the patient is receiving steroids.

A few asthmatic children do not respond to good allergic management and have to have many admissions to hospital and numerous trips to the emergency room. They miss much time at school, have many sleepless nights, create a financial burden for the family and significant emotional stress for themselves and their parents. The point at which prolonged steroid therapy becomes justified depends on how the child and his family react to

the illness. Some children can lead reasonably normal lives in the face of severe asthma; in others, a moderate amount of asthma can be disrupting. There are no absolute indications for continuous steroid therapy, and the decision to initiate it should be made only after careful consideration of the severity of the illness, its effect on the patient and the significant risks involved.

The presence of emotional factors influences the course of disease in any chronic illness and many children with chronic asthma have disturbed personal and family relationships which seem to affect the disease process. Dubo and coworkers,<sup>21</sup> however, were unable to correlate the severity of parent-child disturbed emotional patterns with severity and course of the child's asthma. Steroids which improve the child's respiratory symptoms and relieve the emotional tensions resulting from asthma will have no effect on other primary psychogenic disturbances. In some cases, putting the asthmatic child into a rehabilitation center may be wiser than prolonged steroid therapy.<sup>7</sup> Although nearly all children at these centers are receiving steroid therapy on arrival, a significant number are weaned from the drugs during their stay. It is also often found advisable for the parents to receive psychiatric help while the child is away from home.

#### Therapeutic Regimen

When a decision is made to use corticoid therapy, the type of treatment regimen must be determined. Careful follow-up is mandatory and the problems of adrenal suppression and growth inhibition must be kept in mind. In normal persons, there is a diurnal variation in spontaneous adrenal cortical activity, with the peak in hydroxycorticoid output between midnight and 8 a.m.<sup>18</sup> With small daily doses of exogenous corticoids there will be less adrenal suppression if the entire dose is administered between 8 and 10 a.m. rather than every 6 hours. Exogenous steroids administered "around the clock" in amounts less than the normal daily output will inhibit adrenal function. When long-term steroid therapy is being discontinued, a gradual tapering off will help to minimize the aggravation of symptoms that may occur until the patient's own pituitary-adrenal axis recovers.

An intermittent steroid schedule (given on three successive days of the week, then stopping for four days) has been used extensively in the management of nephrosis.<sup>9</sup> However, Siegel and co-

workers,<sup>53</sup> who used this regimen in a group of allergic children with good results, still found evidence of adrenal suppression on the fourth day off therapy. Harter and coworkers<sup>33</sup> gave one large dose of prednisone every 48 hours before breakfast to a group of 58 adult patients (many of whom had asthma), this dose being the total amount required ordinarily over a two-day period for relief of symptoms. Adrenal suppressive action of the drug was gone after the first 24 hours and the pituitary-adrenal axis returned to normal in the second 24 hours. The anti-inflammatory effect of the drug, however, usually carried the patient through the entire 48-hour period. Harter<sup>34</sup> recently reported that the administration of ACTH injections once a month improved the efficiency of the 48-hour regimen, in some cases permitting reduction of the prednisone dosage. Siegel and coworkers<sup>55</sup> administered betamethasone to a group of asthmatic children at 48-hour intervals and, contrary to the work by Harter's group, demonstrated the occurrence of adrenal suppression in all subjects. Thus, more studies need to be done, using different steroid preparations, since there may be some discrepancy between the anti-inflammatory potency and adrenal suppressive action of the synthetic corticoids. Studies on the growth patterns of children receiving steroids at 48-hour intervals have not been reported.

Steroids administered by inhalation in the form of dexamethasone aerosols can often control symptoms at a dosage level less than that required with oral medication, and in some patients they are the most effective.<sup>15</sup> It was hoped at first that steroid inhalation therapy would circumvent some of the hazards of the corticoids, but adrenal suppression has also been demonstrated in patients receiving aerosols.<sup>54</sup> Parents must be informed of the difference between a steroid and a regular bronchodilator aerosol and should supervise its administration. In the University of California pediatric allergy clinic, where 200 new patients are seen each year with allergic problems of all degrees of severity, six patients are currently receiving long-term steroid therapy. Three of them are receiving dexamethasone aerosols (three to nine puffs per day), and three are receiving prednisone (5 to 20 mg at 48-hour intervals).

It is not necessary to suppress all allergic symptoms at the expense of high steroid dosage. The dose, in conjunction with standard bronchodilator therapy, should enable the child to carry on nor-

mal activity. The parents, however, must know the type and dose of medication the child receives so that in the event of emergency this information can be given to attending medical personnel. In acute stressful situations supplementary exogenous steroids may be necessary.

Regular efforts should be made to reduce the dose. The entire regimen of treatment for allergic disease should be reviewed periodically since there is a tendency for the family to make compromises when the child's clinical symptoms improve. Above all, the child must be closely observed for six to twelve months after the drugs are discontinued, keeping in mind all of the complications of steroid therapy.

In general, the results of prolonged steroid therapy as measured by relief of allergic symptoms have been good. In the series that have been reported, however, the criteria for the initiation of long-term therapy with steroids, and the concomitant allergic regimen, are not always well defined.<sup>41,56,61</sup> There have been conflicting reports regarding prognosis in asthma since the introduction of these agents. Some investigators feel that the morbidity and mortality have both declined<sup>1</sup>; others think that the morbidity has lessened but the mortality has increased.<sup>48</sup>

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